REMARKS

Claims 26, 27, 32, 33, and 37-57 were pending in the instant application. Claims 26, 27 and 36 have been amended and new claims 58-114 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amendments and new claims can be found in the specification of the present application, for example as outlined in the following table:

CLAIM(S)	SUPPORT IN SPECIFICATION
26, 27	page 54, lines 6-8; page 26, line 6
37	page 54, lines 6-8; page 13, lines 5-7
58	page 37, line 24 through page 38, line 3; page 5, lines 31-34; page 12, lines 28-32; page 25, lines 25-30; page 13, lines 3-8
59	page 37, line 24 through page 38, line 3; page 12, lines 28-32; page 25, lines 25-30; page 13, lines 3-8; page 26, line 6
60	page 37, line 24 through page 38, line 3; page 6, lines 5-14; page 13, lines 3-8; page 26, line 6
61	page 37, line 24 through page 38, line 3; page 30, lines 27-31; page 12, lines 28-32; page 25, lines 25-30; page 26, line 6; page 13, lines 3-8
62	page 25, lines 25-28
63	page 37, line 24 through page 38, line 3; page 13, lines 3-8; page 54, lines 6-8; page 26, line 6
64	page 37, line 24 through page 38, line 3; page 13, lines 3-8; page 26, line 6; page 25, lines 25-28
65	page 25, lines 25-28
66	page 5, line 36 through page 6, line 4; page 5, lines 27-31; page 13, lines 3-8
67, 68	page 7, lines 23-26

CLAIM(S)	SUPPORT IN SPECIFICATION
69, 75	page 5, lines 25-26
70, 76	page 24, line 29
71, 77	page 24, line 29
72, 78	page 25, lines 1-6
73, 74, 79, 80	page 34, lines 5-6
81, 82	page 9, lines 29-30
83, 84, 85	page 5, lines 27-31
86-93	page 13, lines 3-8
94-97	page 37, line 39 through page 38, line 3
98-114	pages 39-40 (table 1)

No new matter has been added.

Upon entry of the amendments made herein, claims 26, 27, 32, 33, and 37-114 will be pending in the present application.

INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella for the courtesy of the recent interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants present this interview Summary Record of the interview of September 24, 2002 ("the Interview") between Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella, Applicant Dr. H. Perry Fell, and Applicants' representatives, Adriane M. Antler and Muna Abu-Shaar, in connection with the above-referenced application. During the Interview, the outstanding Office Action was discussed.

Applicants' representative, Attorney Adriane M. Antler, discussed why the recitation in the Amendment of February 19, 2002 of "human antibody" in claims 49 and 56 did not introduce new matter. In particular, Dr. Antler noted that the amendment was supported by the specification, for example at page 25, lines 1-6. Supervisory Patent

Examiner Caputa and Examiner Canella agreed that claims 49 and 56 were supported by the specification.

Applicant and Applicants' representative also presented arguments as to why the instantly claimed invention was not made obvious by the prior art relied upon by Examiner Canella in the instant Office Action. Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella agreed that the obviousness rejections would be overcome as long as the claims recited methods of treatment using molecules with structural characteristics (*i.e.*, either the S2C6 heavy chain CDR or variable region sequences or closely related sequences) or functional characteristics (*i.e.*, increasing the binding of CD40 ligand to cell surface CD40 on B cells) that distinguished the molecules from prior art antibodies.

Details of these arguments are presented below.

THE OBJECTION UNDER 35 U.S.C. § 132 AND REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

The Examiner has objected to the Amendment of February 19, 2002, and rejected claims 49 and 56 under 35 U.S.C. § 112, first paragraph, for lack of written description, because new claims 49 and 56 allegedly introduce new matter. In particular, the Examiner states that the recitation of "human antibody" lacks sufficient support in the specification. Applicants respectfully disagree.

Applicants note that support for human antibodies can be found in the specification, for example at page 25, lines 1-6. Thus, as agreed upon by Supervisory Examiner Caputa and Examiner Canella during the Interview, the language of claims 49 and 56 is fully supported by the specification as filed.

In view of the foregoing, Applicants submit that the objection to claims 49 and 56 under 35 U.S.C. § 132, and the rejection of these claims under 35 U.S.C. § 112, first paragraph, for lack of written description, have been obviated and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

All pending claims are rejected under 35 U.S.C. § 103(a) as obvious over the prior art. In particular, claims 37, 41, 44, 45, 50 and 51 are rejected under 35 U.S.C. § 103(a) as obvious over Hirano *et al.*, 1999, Blood 9:2999-3007 ("Hirano") in view of Pound

et al., 1999, International Immunology 11:11-20 ("Pound"). Claims 37, 41, 44-48, 50 and 51 are rejected under 35 U.S.C. § 103(a) as obvious over Hirano and Pound in view of U.S. Patent No. 5,874,082 to de Boer ("de Boer"). Claims 26, 26, 32, 33, 37-48, 50-55 and 57 are rejected under 35 U.S.C. § 103(a) as obvious over Francisco *et al.*, 1997, J. Biol. Chem. 272(39):24165-9 ("Francisco") in view of Hirano, Paulie *et al.*, 1989, J. Immunol. 142(2):590-5 ("Paulie"), and de Boer. Applicants respectfully disagree. Prior to addressing the substance of these rejections, Applicants present a summary of the relevant case law regarding obviousness.

The Law of Obviousness

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation for* the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reaches the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir 1988).

"Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir.1999), abrogated on other grounds, citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). In particular, the Examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Care must be taken to avoid hindsight reconstruction by using Applicants' disclosure "as a guide through the maze of prior art references, combining the right references in the right way so

as to achieve the result" of the claims in question. *Grain Processing Corporation v. American Maize-Products Company*, 840 F.2d 902, 907 (Fed. Cir. 1988), citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983).

Applicants submit that, the Examiner, in raising the obviousness rejections, is employing, perhaps unconsciously, a hindsight reconstruction without casting her mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction does not meet the legal standard for obviousness. Each of the combinations of references cited by the Examiner is discussed in turn below to demonstrate that, standing in the shoes of the Applicants at the time the present application was filed, there was no suggestion of or motivation in the art to practice the claimed invention.

I. The Rejection of Claims 37, 41, 44, 45, 50 and 51 over Hirano in View of Pound Should Be Withdrawn

Claims 37, 41, 44, 45, 50 and 51 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Hirano *et al.*, 1999, Blood 9:2999-3007 ("Hirano") in view of Pound *et al.*, 1999, International Immunology 11:11-20 ("Pound"). According to the Examiner, Hirano teaches the inhibition of "human breast carcinoma cells by a soluble CD40 ligand" and that "preliminary data indicated that ovarian carcinomas and bladder carcinomas are also inhibited in vitro by the CD40 ligand, suggesting that CD40 stimulation may be beneficial in the treatment of these tumors in vivo." The Examiner further states that Hirano suggests "a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, wherein the anti-CD40 antibody is not an antagonist of the CD40 receptor in order to assess synergism between the CD40 ligand and the anti-CD40 antibody." With respect to Pound, the Examiner states that Pound teaches "the monoclonal antibody of 5C3 which increases the binding of the CD40 ligand to the CD40 receptor on T-cells." The Examiner concludes that it would have been *prima facie* obvious "to combine the 5C3 antibody with the CD40 ligand and administer the combination" to treat certain carcinomas "with a reasonable expectation of success by the teachings of Hirano suggesting the combination of CD40 ligand with an antibody which activates the CD40 receptor ... and the teachings of Pound on the 5C3 antibody which increases the binding of the CD40 ligand to the CD40 receptor." Applicants respectfully disagree for the reasons discussed below.

First, Applicants note that claim 37, as amended herein, and therefore claims 41, 44, 45, 50 and 51 dependent thereon, recite a method of treating or preventing cancer comprising administering a molecule that binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and CD40 ligand.

With respect to Hirano, while Hirano teaches that CD40 ligand inhibits the growth of breast cancer cells, Hirano does not teach that an anti-CD40 antibody having the characteristics of S2C6, *i.e.*, the ability to increase the binding of cell surface CD40 on B cells to CD40 ligand, can be useful to treat cancer. In particular, Hirano, while promoting the advantages of soluble CD40 ligand over monoclonal antibodies (Hirano at 3006, left column, third paragraph), states that "anti-CD40 MoAbs [other than M3] *may* be able to exert growth-inhibitory effects on carcinoma cells. It may also be of interest to combine the ligand with anti-CD40 MoAbs to assess potential synergistic effects" (Hirano at 3006, left column, first paragraph). Contrary to the Examiner's conclusion that Hirano's suggestion of combining CD40 ligand with a non-antagonistic anti-CD40 antibody provides a reasonable expectation that the combination would be successful in treating carcinoma, a general invitation to experiment without specific teachings on how to achieve the desired result does not provide a reasonable expectation of success and therefore does not raise a *prima facie* case of obviousness. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986). At best, Hirano provides an invitation to experiment combining CD40 ligand with non-antagonist CD40 antibodies. As discussed above, Hirano does not teach that an anti-CD40 antibody having the characteristics of S2C6, *i.e.*, the ability to increase the binding of cell surface CD40 on B cells to CD40 ligand, alone or in combination with CD40 ligand, can be useful for treating cancer. Accordingly, in view of the applicable case law, Hirano does not render obvious the presently claimed invention of claims 37, 41, 44, 45, 50 and 51.

Pound does not remedy the deficiencies of Hirano. In particular, Pound does not teach, suggest, provide motivation for, treating cancer by administering to a patient a composition comprising a molecule that increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and CD40 ligand. Pound compares various characteristics of eight different anti-CD40 monoclonal antibodies, including S2C6. Pound describes cross-blocking experiments among the antibodies, the antibodies' ability to block binding of soluble CD40 to cell surface CD40 ligand on T cells, and rescue of B cells from

apoptosis, and in the discussion focuses on mechanisms of CD40 receptor signaling. Nowhere does Pound suggest or provide motivation for using any of the antibodies, alone or with CD40 ligand, to treat cancer. Pound, accordingly, does not render obvious the invention presently claimed in claims 37, 41, 44, 45, 50 and 51.

The Examiner believes that Hirano suggests using an antibody such as 5C3, as described by Pound, in combination with CD40 ligand, to treat carcinomas. Applicants have discussed why the suggestion of Hirano is no more than an invitation to experiment using combinations of CD40 antibody and CD40 ligand. However, even assuming *arguendo* that the combination of Hirano and Pound suggested treating carcinoma by administering a combination of CD40 ligand and the anti-CD40 antibody 5C3, a conclusion that the presently claimed invention is obvious still cannot be reached. As Applicants and/or their representatives pointed out to the Examiners during the interviews of February 7, 2002 and September 24, 2002, the experiments of Pound show that 5C3 is clearly distinct from the S2C6-like anti-CD40 molecules recited in the methods of claims 37, 41, 44, 45, 50 and 51. Specifically, Pound demonstrates that the binding activities of S2C6 and 5C3 are dramatically distinct when compared side by side.

In particular, the Examiner's attention is directed to Table 1 of Pound, which compares the effects of various antibodies on the binding of CD40 ligand on the surface of T cells to a soluble CD40-immunoglobulin fusion protein ("CD40-Fc") (NOT to cell surface CD40 on B cells), and the inhibitory effects of the eight anti-CD40 antibodies in the employed in the Pound experiments on the binding of S2C6 to cell surface CD40. Where the effect of the various antibodies on the binding of CD40 ligand to soluble CD40-Fc was examined, the CD40-Fc was preincubated with the test antibody, and the ability of the test antibody-CD40-Fc complex to bind to CD40 ligand on activated T cells was measured relative to CD40-Fc preincubated with a control antibody (see section entitled "Inhibition of binding of soluble CD40 to CD40L on T cells" at page 12, right hand column). Where the effect of the various antibodies on the binding of S2C6 to cell surface was examined, resting B cells were preincubated with the test antibody, after which time the cells were incubated with S2C6. The ability of the pre-bound test antibody to inhibit S2C6 binding to the resting B cells was measured (see section entitled "Inhibition of binding of CD40 mAb S2C6 to CD40 on B cells" at page 13, left hand column).

Under these experimental conditions, S2C6 decreased CD40-Fc binding to CD40 ligand on T cells by approximately 82%, whereas 5C3 increased CD40-Fc binding to CD40 ligand on T cells by approximately 32% (Table 1, first line of data). These data provide conclusive evidence that S2C6 and 5C3 have different epitope specificities, and therefore could not share the same or closely related set of heavy chain CDRs. Furthermore, binding of 5C3 to B cells did not preclude to a significant degree (22%) the subsequent binding of S2C6 to cell surface CD40 (Table 1, second line of data), indicating that CD40 can simultaneously bind to S2C6 and 5C3. This provides yet further evidence that the two antibodies are distinct both functionally and structurally. The sum of the data presented in Pound demonstrates, as depicted in Figure 7 of Pound, distinct epitope specificities of S2C6 and 5C3. Accordingly, even if one could glean from Hirano and Pound together a suggestion to use a combination of CD40 ligand and 5C3 to treat carcinomas, the clearly different characteristics of S2C6 described in Pound would teach away from using S2C6-like antibodies and CD40 ligand to treat carcinomas.

In view of the foregoing, Applicants submit that the rejection of claims 37, 41, 44, 45, 50 and 51 under 35 U.S.C. § 103 has been obviated and should be withdrawn.

II. The Rejection of Claims 37, 41, 44-48, 50 and 51 over Hirano and Pound in view of de Boer Should Be Withdrawn

Claims 37, 41, 44-48, 50 and 51 are rejected under 35 U.S.C. § 103(a), allegedly as obvious over Hirano and Pound in view of U.S. Patent No. 5,874,082 to de Boer ("de Boer"). In particular, the Examiner states that the claims are obvious over Hirano and Pound as applied to claims 37, 41, 44, 45, 50 and 51 and further in view of de Boer, which teaches humanization of the anti-CD40 antibodies 5D12, 3A8, and 3C6. The Examiner concludes that de Boer's teaching of humanized forms of the anti-CD40 antibodies 5D12, 3A8, and 3C6, rendering it *prima facie* obvious for one of skill in the art to "humanize the 5C3 antibody for administration to humans," thereby rendering obvious claims 37, 41, 44-48, 50 and 51.

Applicants note that U.S. Patent No. 5,874,082 does *not* disclose humanized forms of the anti-CD40 antibodies 5D12, 3A8, and 3C6. Applicants assume that the rejection is based on U.S. Patent No. 5,677,165 to de Boer ("de Boer II"), which has been cited by the Examiner in related applications, and will treat the rejection as such.

First, Applicants again note that claim 37 as amended herein, and therefore claims 41, 44-48, 50 and 51 dependent thereon, recite a method of treating or preventing cancer by administering a molecule that binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and CD40 ligand.

Further, as discussed above, Applicants submit that the suggestion of Hirano which, when read in the context of the entire reference, merely presents an invitation to experiment by combining non-antagonistic anti-CD40 antibodies with CD40 ligand. As further noted above, Pound fails to remedy the deficiencies of Hirano, as Pound does not suggest or provide motivation for use of anti-CD40 antibodies that increase the binding of CD40 ligand to cell surface CD40 on B cells, alone or in combination with CD40 ligand, for the treatment of cancer, let alone the use of such antibodies that increase the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% for the treatment or prevention of cancer. Thus, neither reference suggests the therapeutic use of S2C6-like molecules for the treatment or prevention of cancer.

de Boer II does not remedy the deficiencies of Hirano or Pound. de Boer II describes the anti-CD40 antibodies 5D12, 3A8, and 3C6, a class of antibodies which prevents the growth and differentiation of B cells and blocks the CD40-CD40L interactions (see, *e.g.*, *de Boer II* at Column 12, line 67 through column 13, line 1, characterizing the de Boer II antibodies as "blocking the CD40-CD40 ligand interaction"). This blocking activity is clearly in the context of cell surface CD40 on B cells, as the blocking assays of de Boer II measured the inhibition of T-cell-induced B-cell proliferation (*de Boer* Example 5, columns 18-19). The teachings of de Boer II of humanizing 5D12 and suggesting the humanization of 3A8 and 3C6 are based on their inhibitory property which, according to de Boer, makes these antibodies useful to treat disorders characterized by overproduction of antibodies, such as autoimmune disorders. *de Boer II* at column 3, lines 6-8 and 52-54. Accordingly, de Boer II does not remedy the deficiencies of Pound or Hirano, as de Boer II does not suggest or provide motivation for humanization of antibodies that promote proliferation of normal B cells or increase the binding of CD40 ligand to cell surface CD40 on B cells, let alone the use of such antibodies and CD40 ligand for the treatment or prevention of cancer.

In view of the foregoing, Applicants submit that the rejection of claims 37, 41, 44-48, 50 and 51 under 35 U.S.C. § 103 are obviated and should be withdrawn.

III. The Rejection of Claims 26, 27, 32, 33, 37-48, 50-55 and 57 over Francisco, Paulie, Hirano, and de Boer Should Be Withdrawn

Claims 26, 27, 32, 33, 37-48, 50-55 and 57 are rejected under 35 U.S.C. § 103(a), allegedly as obvious over Francisco *et al.*, 1997, J. Biol. Chem. 272(39):24165-9 ("Francisco") in view of Hirano, Paulie *et al.*, 1989, J. Immunol. 142(2):590-5 ("Paulie"), and de Boer (again, as discussed above, this assumed to be de Boer II and will be treated as such).

The rejected claims (as amended herein) are drawn to methods of treatment or prevention of cancer comprising administering to a patient a molecule that increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and (i) binds CD40, comprises one or more CDR or variable region sequences of S2C6 and comprises a human constant domain (claim 26 and claims dependent thereon); (ii) competes with the antibody S2C6 for binding to CD40 and comprises a human constant domain (claim 27 and claims dependent thereon), or (iii) binds to CD40 and is used in combination with CD40 ligand.

According to the Examiner, Francisco teaches single chain immunotoxins of the monoclonal anti-CD40 antibody G28-5 fused to bryodin and pseudomonas exotoxin, to which certain carcinomas or B cell malignancies were sensitive; Paulie teaches that "S2C6 antibody binds at a proximal epitope to that bound by the G28-5 antibody" and that S2C6 and G28-5 bind similar cell types; Hirano teaches that administration of "anti-CD40 antibodies" had anti-tumor effects and suggests a composition comprising non-antagonistic antibody and CD40 ligand; and de Boer teaches humanized forms of the anti-CD40 antibodies 5D12, 3A8, and 3C6. The Examiner then concludes that Francisco would provide the skilled artisan with the motivation to "substitute the variable heavy and light chains of the S2C6 antibody for the variable heavy and light chains of the G28-5 antibody" in the G28-5 immunotoxins with a reasonable expectation of success based on the teachings of Paulie. The Examiner also concludes that Francisco, Paulie, Hirano and de Boer would provide the skilled artisan with the motivation, with a reasonable expectation of success, to humanize S2C6 for use in combination with CD40 ligand to treat cancer. Applicants disagree for the reasons presented below.

Francisco teaches the production of a single chain immunotoxin, BD1-G28-5 sFv, comprising the heavy and light chain variable regions of the anti-CD40 antibody G28-5 and bryodin 1. The immunotoxin was found to bind to soluble CD40 and was cytotoxic to B cell malignancies (Francisco at page 24167, bottom left column and entire right column), and cytotoxic to monocytes activated with IFN-γ (but not to non-activated monocytes) (Francisco at page 24168, top left column). The immunotoxin was found to be ineffective in killing carcinoma cells (Francisco at page 24168, bottom left column). In the discussion, Francisco compares and contrasts the activities of BD1-G28-5 sFv with the earlier-published G28-5-PE40 sFv, a G28-5 based immunotoxin comprising *Pseudomonas* exotoxin. BD1-G28-5 was comparable to G28-5-PE40 in all activities, with the exception of a failure to exert a cytotoxic effect on carcinoma cells, in contrast to G28-5-PE40. Francisco's teaching are based on G28-5-based immunotoxins, and does not teach, suggest or provide any motivation for treating cancer with therapeutics having the CDR or variable region sequences or sequences related thereto, or functional characteristics of S2C6.

Paulie does not remedy the deficiencies of Francisco. Paulie describes the requirements of B cell stimulation by anti-CD40 antibodies. Paulie also describes that S2C6 induces B cell proliferation and that both G28-5 ad S2C6 recognize CD40 on B lymphocytes, and can block binding of each other. Paulie describes ELISA experiments to characterize antibodies other than S2C6 suspected to bind to B cell antigens. Of these antibodies, G28-5 bound CD40. S2C6 and G28-5 displayed competitive inhibition of the binding of one another; however, G28-5 was more effective, leading Paulie to suggest that G28-5 has higher affinity to CD40 than does S2C6 (Paulie at page 592, right column). As would be expected of two anti-CD40 antibodies, similar staining profiles against a panel of cell lines were observed for the two antibodies. Nothing in the findings of Paulie suggests production of fusion proteins comprising sequences from S2C6. If anything, Paulie teaches against the use of S2C6 for therapeutic purposes, since it implies that S2C6 can promote the proliferation of cancer cells (*see* Paulie at page 594, bottom left column). Accordingly, Paulie, whether alone or in combination with Francisco, does not teach, suggest or provide motivation for cloning S2C6, let alone motivation for making molecules comprising the heavy chain CDR or variable regions of S2C6 or closely related sequences fused to non-antibody molecules, much less the use of such molecules for the prevention or treatment of cancer. To find otherwise, when none of the reference cited by the Examiner "convey or

suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore*, 721 F.2d at 1553.

As discussed above, neither Francisco nor Paulie provides any suggestion of a use of S2C6-like molecules to treat cancer. Indeed, despite the allegations made by the Examiner that the prior art teaches that G28-5 and S2C6 are similar and that, accordingly, one of skill in the art would be motivated by the teachings of Francisco and Paulie to make recombinant molecules comprising the heavy chain CDR or variable regions of S2C6, the Examiner ignores (i) a lack of any suggestion by Francisco to make immunotoxins other than the G28-5-based immunotoxin taught therein; as well as the teachings of Paulie (ii) that G28-5 has a higher binding affinity to CD40 than S2C6 and (iii) that making recombinant molecules comprising the CD40 for the purpose of cancer therapy is likely undesirable given Paulie's findings that CD40-expressing cancer cell lines can be made to "propagate in response to antibody treatment" without preactivating agents.

Applicants take this opportunity to point out the very different properties of G28-5 and S2C6, which would also lead one of skill in the art away from cloning S2C6 and using it therapeutically or prophylactically on the basis of the teachings of Francisco regarding G28-5-based immunotoxins. First, with respect to the ability to promote binding of CD40 ligand to CD40, Applicants note in the specification, in particular at page 54, lines 24-29, that "[t]hese data indicate that S2C6 differs surprisingly from G28-5... in its ability to increase CD40L/CD40 interaction." Further, not only does Applicants' specification teach that G28-5 and S2C6 differ greatly in the ability to promote the binding of CD40 ligand to CD40, but so does the art. In particular, Pound, discussed in Sections I and II above, teaches that S2C6 and G28-5 are vastly different with respect to their ability to promote B cell proliferation in the presence of soluble trimeric CD40 ligand (sCD40LT): S2C6 and sCD40LT have synergistic stimulatory effects on proliferation of resting B cells, whereas G28-5 has no evidence of such a cooperative interaction with sCD40LT. Pound also concludes that G28-5 and S2C6 have distinct epitope specificities (see Figure 7 of Pound).

Hirano does not remedy the deficiencies of Francisco or Paulie. As discussed above, Hirano at best provides a general suggestion to combine CD40 ligand with non-antagonistic CD40 antibodies in treating cancer. Hirano does not specifically teach, suggest or provide motivation for the claimed methods, *i.e.*, methods of treating or

preventing cancer using a molecule that increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and (i) binds CD40, comprises one or more CDR or variable region sequences of S2C6 and comprises a human constant domain (claim 26 and claims dependent thereon); (ii) competes with the antibody S2C6 for binding to CD40 and comprises a human constant domain (claim 27 and claims dependent thereon), or (iii) binds to CD40 and is used in combination with CD40 ligand.

de Boer does not remedy the deficiencies of Francisco, Paulie or Hirano. If anything, de Boer teaches away from the presently claimed invention by teaching the humanization of CD40 antibodies that *block* rather than promote the CD40-CD40 ligand interaction. Like Hirano, de Boer does not specifically teach, suggest or provide motivation for the claimed methods, *i.e.*, methods of treating or preventing cancer using a molecule that increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and (i) binds CD40, comprises one or more CDR or variable region sequences of S2C6 and comprises a human constant domain (claim 26 and claims dependent thereon); (ii) competes with the antibody S2C6 for binding to CD40 and comprises a human constant domain (claim 27 and claims dependent thereon), or (iii) binds to CD40 and is used in combination with CD40 ligand. Accordingly, the rejection is improper and should be withdrawn.

Further, in making the argument that methods of treatment of cancer using molecules comprising CDR or heavy chain variable region sequences of S2C6 (as claimed in claim 26 and claims dependent thereon) are obvious, the Examiner follows essentially the same obviousness analysis disallowed in *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995). Specifically, as stated by the Federal Circuit, the existence of a general method of isolating molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the structures of the claimed molecules. *Deuel*, 51 F.3d at 1557-59. Thus even assuming, *arguendo*, that there were such a suggestion or motivation in the prior art "as a whole" to make molecules comprising the CDRs or variable region of S2C6 for treating cancer, a finding of obviousness is improper without a suggestion of the specific sequences encompassed by the method of claim 26, which none of the references cited by the Examiner provides.

Accordingly, Applicants submit that the rejection of claims 26, 27, 32, 33, 37-48, 50-55 and 57 under 35 U.S.C. § 103(a) as obvious over Francisco, Paulie, Hirano, and de Boer has been obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.

Respectfully submitted,

Date: November 21, 2002

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Exhibit A
U.S. Application No. 09/724,530
Attorney Docket No. 9632-012
Marked Up Copy of Amended Claims

26. (Amended) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a molecule comprising SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10, which molecule (i) [immunospecifically] binds CD40, (ii) increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, and (iii) comprises [one or more substitutions or insertions in primary amino acid sequence relative to native monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110] a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

27. (Amended) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a purified protein, which protein (i) competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110, (ii) increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, and (iii) comprises [one or more substitutions or insertions in primary amino acid sequence relative to native monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110] a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

37. (Amended) A method for the treatment or prevention of cancer or an immune disorder in a subject comprising administering to the subject, in an amount effective for said treatment or prevention: (a) a molecule that immunospecifically binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%; and (b) CD40 ligand.

Exhibit B
U.S. Application No. 09/724,530
Attorney Docket No. 9632-012
Claim as Pending Following Entry of Amendment filed November 22, 2002

26. (Amended) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a molecule comprising SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10, which molecule (i) binds CD40, (ii) increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, and (iii) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

27. (Amended) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a purified protein, which protein (i) competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110, (ii) increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%, and (iii) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

32. The method of any one of claims 26 or 27 further comprising administering CD40 ligand to the subject.

33. The method of any one of claims 26 or 27 in which the subject is a human.

37. (Amended) A method for the treatment or prevention of cancer or an immune disorder in a subject comprising administering to the subject, in an amount effective for said treatment or prevention: (a) a molecule that immunospecifically binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%; and (b) CD40 ligand.

38. The method of claim 26, wherein the molecule is conjugated to a chemotherapeutic agent.

39. The method of claim 27, wherein the protein is conjugated to a chemotherapeutic agent.

40. The method of claim 37, wherein the molecule is conjugated to a chemotherapeutic agent.

41. The method of claim 26 or 37, wherein the molecule is purified.

42. The method of any one of claims 38-40, where the subject is a human.

43. The method of claim 26, wherein the molecule is purified, further comprising administering CD40 ligand to the subject.

44. The method of claim 26 or 37, wherein the molecule is a protein.

45. The method of claim 44, wherein the protein is an antibody.

46. The method of claim 45, wherein the antibody comprises a human constant region.

47. The method of claim 46, wherein the antibody is a chimeric antibody.

48. The method of claim 46, wherein the antibody is a humanized antibody.

49. The method of claim 46, wherein the antibody is a human antibody.

50. The method of claim 45, wherein the antibody is purified.

51. The method of claim 50, further comprising administering CD40 ligand to the subject.

52. The method of claim 27, wherein the protein is an antibody.

53. The method of claim 52, wherein the antibody comprises a human constant region.

54. The method of claim 53, wherein the antibody is a chimeric antibody.

55. The method of claim 53, wherein the antibody is a humanized antibody.

56. The method of claim 53, wherein the antibody is a human antibody.

57. The method of claim 52, further comprising administering CD40 ligand to the subject.

58. (New) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a molecule comprising SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, which molecule (a) binds CD40, and (b) is a fusion protein comprising the amino acid sequence of a second molecule that is not an antibody, which amount is effective for the treatment or prevention of cancer.

59. (New) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a molecule comprising SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, which molecule (a) binds CD40, and (b) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

60. (New) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a protein comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:7 as determined by use of the BLASTp computer program, which protein (a) binds CD40; and (b) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

61. (New) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a protein comprising an amino acid sequence that comprises regions having at least 80% identity to SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:10, respectively, as determined by use of the BLASTp computer program, which protein (a) binds CD40; and (b) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

62. (New) The method of claim 61, wherein the protein comprises at least 2 CDR sequences selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO 10.

63. (New) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a molecule that (a) binds to CD40; (b) increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%; and (c) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

64. (New) A method for the treatment or prevention of cancer in a subject comprising:

administering to the subject an amount of a molecule which (a) competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110; (b) comprises at least 2 CDR

sequences selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO 10; and (c) comprises a human immunoglobulin constant domain, which amount is effective for the treatment or prevention of cancer.

65. (New) The method of claim 64, wherein the molecule comprises SEQ ID NO:8 and SEQ ID NO:10.

66. (New) The method of claim 58 or 59, wherein the molecule comprises an amino acid sequence of bryodin (BD1) fused to SEQ ID NO:7 fused to SEQ ID NO:2.

67. (New) The method of any of claims 58, 59, 60, and 63-66, wherein the molecule is purified.

68. (New) The method of claim 61 or 62, wherein the molecule is purified.

69. (New) The method of any of claims 58, 59, 60, and 63-66, wherein the molecule is an antibody.

70. (New) The method of claim 69, wherein the antibody is a chimeric antibody.

71. (New) The method of claim 69, wherein the antibody is a humanized antibody.

72. (New) The method of claim 69, wherein the antibody is a human antibody.

73. (New) The method of any of claims 58, 59, 60, and 63-66, wherein the molecule is conjugated to a chemotherapeutic agent.

74. (New) The method of claim 69, wherein the antibody is conjugated to a chemotherapeutic agent.

75. (New) The method of claim 61 or 62, wherein the molecule is an antibody.

76. (New) The method of claim 75, wherein the antibody is a chimeric antibody.

77. (New) The method of claim 75, wherein the antibody is a humanized antibody.

78. (New) The method of claim 75, wherein the antibody is a human antibody.

79. (New) The method of claim 61 or 62, wherein the molecule is conjugated to a chemotherapeutic agent.

80. (New) The method of claim 75, wherein the antibody is conjugated to a chemotherapeutic agent.

81. (New) The method of any of claims 58, 59, 60, and 63-66, further comprising administering CD40 ligand to the subject.

82. (New) The method of claim 61 or 62, further comprising administering CD40 ligand to the subject.

83. (New) The method of claim 58 or 59, wherein the molecule comprises SEQ ID NO:7.

84. (New) The method of claim 58 or 59, wherein the molecule further comprises SEQ ID NO:2.

85. (New) The method of claim 83, wherein the molecule further comprises SEQ ID NO:2.

86. (New) The method of claim 60 or 61, wherein the protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%.

87. (New) The method of claim 27, 60 or 61, wherein the protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 50%.

88. (New) The method of claim 27, 60 or 61, wherein the protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 60%.

89. (New) The method of claim 27, 60 or 61, wherein the protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 65%.

90. (New) The method of claim 58, 59 or 64, wherein the molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%.

91. (New) The method of claim 26, 37, 58, 59, 63 or 64, wherein the molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 50%.

92. (New) The method of claim 26, 37, 58, 59, 63 or 64, wherein the molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 60%.

93. (New) The method of claim 26, 37, 58, 59, 63 or 64, wherein the molecule increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 65%.

94. (New) The method of claim 26, 37, 58, 59, 63 or 64, wherein the method is for treatment of cancer, the subject has cancer, and the cancer is a hematologic malignancy.

95. (New) The method of claim 87, wherein the method is for treatment of cancer, the subject has cancer, and the cancer is a hematologic malignancy.

96. (New) The method of claim 91, wherein the method is for treatment of cancer, the subject has cancer, and the cancer is a hematologic malignancy.

97. (New) The method of claim 26, 37, 58, 59, 63 or 64, wherein the method is for treatment of cancer, the subject has cancer, and the cancer is a carcinoma.

98. (New) The method of claim 87, wherein the method is for treatment of cancer, the subject has cancer, and the cancer is a carcinoma.

99. (New) The method of claim 91, wherein the method is for treatment of cancer, the subject has cancer, and the cancer is a carcinoma.

100. (New) The method of claim 94, wherein the hematologic malignancy is chronic leukemia, lymphoma, or multiple myeloma.

101. (New) The method of claim 95, wherein the hematologic malignancy is chronic leukemia, lymphoma, or multiple myeloma.

102. (New) The method of claim 96, wherein the hematologic malignancy is chronic leukemia, lymphoma, or multiple myeloma.

103. (New) The method of claim 100, wherein the chronic leukemia is chronic myelocytic leukemia or chronic lymphocytic leukemia.

104. (New) The method of claim 101, wherein the chronic leukemia is chronic myelocytic leukemia or chronic lymphocytic leukemia.

105. (New) The method of claim 102, wherein the chronic leukemia is chronic myelocytic leukemia or chronic lymphocytic leukemia.

106. (New) The method of claim 100, wherein the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma.

107. (New) The method of claim 101, wherein the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma.

108. (New) The method of claim 102, wherein the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma.

109. (New) The method of claim 97, wherein the carcinoma is ovarian cancer, lung carcinoma or bladder carcinoma.

110. (New) The method of claim 98, wherein the carcinoma is ovarian cancer, lung carcinoma or bladder carcinoma.

111. (New) The method of claim 99, wherein the carcinoma is ovarian cancer, lung carcinoma or bladder carcinoma.

112. (New) The method of claim 109, wherein the lung carcinoma is small cell lung carcinoma or non-small cell lung carcinoma.

113. (New) The method of claim 110, wherein the lung carcinoma is small cell lung carcinoma or non-small cell lung carcinoma.

114. (New) The method of claim 111, wherein the lung carcinoma is small cell lung carcinoma or non-small cell lung carcinoma.